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Original Article

Association between CT-Detected Coronary Artery Calcification and Serum Homocysteine Level in Asymptomatic Adults

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ABSTRACT

The association between CT-detected CAC and serum homocysteine levels in asymptomatic adults may provide valuable insights into the pathophysiological mechanisms underlying subclinical atherosclerosis. **Objectives:** To determine the association between CT-detected coronary artery calcification and serum homocysteine levels in the asymptomatic Pakistani population. **Methods:** A cross-sectional analytical study was conducted on 384 asymptomatic Pakistani adults aged 30–65 years. Coronary artery calcification was assessed using non-contrast CT (Agatston score), and serum homocysteine levels were measured. Associations were analyzed using descriptive statistics and Pearson correlation using SPSS. **Results:** Among 384 asymptomatic adults, coronary artery calcification (CAC) was detected in 41.7% of participants. Individuals with CAC had significantly higher serum homocysteine levels compared to those without calcification ($p < 0.001$). Serum homocysteine increased progressively with CAC severity and showed a significant positive correlation with CAC score. Statistical testing demonstrated that serum homocysteine was significantly associated with coronary artery calcification after adjusting for traditional cardiovascular risk factors. **Conclusions:** Elevated serum homocysteine was independently associated with the presence and severity of CT-detected coronary artery calcification in asymptomatic adults. These findings suggest that homocysteine may serve as a useful biomarker for identifying individuals at increased risk of subclinical coronary atherosclerosis.

INTRODUCTION

Coronary artery disease (CAD) is one of the most common causes of morbidity and mortality globally and often progresses asymptomatically before clinical symptoms start to appear [1]. For effective prevention and risk stratification of subclinical atherosclerosis, especially in asymptomatic individuals, it is crucial to identify it as early as possible [2]. Coronary artery calcification (CAC) can serve as an indicator of coronary atherosclerotic burden and can be detected via non-invasive techniques such as computed tomography (CT) [3]. In individuals without a symptomatic cardiovascular risk factor or overt disease, the extent of CAC independently predicts adverse cardiovascular events and correlates strongly with the total burden of the disease [4]. Using CT, CAC can be calculated using the coronary artery calcium score (CACS). Future risk of any adverse cardiovascular event and atherosclerosis (not clinically evident) can be detected early via CACS, especially in the asymptomatic population for primary prevention [5]. CAC detects inflammation, any chronic vascular injury, and osteogenic changes of

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vascular smooth cells within plaques of atherosclerosis [6]. Scoring of CAC based on CT-scan (non-contrast) is mostly quantified with the help of the Agatston method. It is a highly reliable and reproducible scoring system for the assessment of coronary risk. The likelihood of an adverse cardiovascular event increases with higher scores on CAC [7]. Assessment using CAC helps in terms of prognostic value apart from the traditional cardiovascular risk factors. This makes it specifically valuable in an asymptomatic population, wherein conventional risk scorings might either under- or over-estimate the true burden of disease [8]. Sulfur-containing amino acid homocysteine, formed during the metabolism of methionine, has been identified as a distinct risk factor for atherosclerosis and cardiovascular disease [9]. Elevated blood homocysteine levels are believed to induce oxidative stress, prothrombotic states, vascular smooth muscle proliferation, and endothelial dysfunction, all of which contribute to the onset and advancement of atherosclerosis [10]. Homocysteine is more prevalent in calcified atheroma than in non-calcified lesions and increases the production of reactive oxygen species and inflammatory signals. Although hyperhomocysteinemia has been associated with increased cardiovascular risk, its role in the initiation and progression of coronary calcification remains incompletely understood [11]. Homocysteine reduces nitric oxide, disrupts antioxidant systems, and increases reactive oxygen species (ROS), driving endothelial activation and lipid oxidation, early steps in plaque formation. In hyperhomocysteinemia, plaques are larger, more inflammatory, and less collagen-rich. Homocysteine activates NLRP3(nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) and induces macrophage pyroptosis via ER stress, mitochondrial dysfunction, and calcium dysregulation, and stimulates vascular smooth muscle cell (VSMC) proliferation and pro-atherogenic gene programs, partly via miRNA-mediated and methylation [12]. Reactive metabolites like homocysteine-thiolactone and N-homocysteinylated proteins promote clot formation and impair fibrinolysis, adding a thrombotic layer to established plaque disease. In patients with angina and non-obstructive CAD, higher homocysteine (>9 µmol/L, upper quartile) independently predicts coronary microvascular endothelial dysfunction, a marker of early atherosclerosis [13]. Previous literature suggests a potential link between elevated homocysteine levels and arterial calcification. However, findings have been inconsistent, particularly in asymptomatic adults, where the interplay between biochemical markers and structural vascular changes is more understated. Moreover, the majority of existing studies have focused on symptomatic patients or those with established cardiovascular disease, limiting their applicability to early disease detection and primary prevention [14]. Understanding the association between CT-detected CAC and serum homocysteine levels in asymptomatic adults may provide valuable insights into the pathophysiological mechanisms underlying subclinical atherosclerosis. Such an association could support the combined use of imaging biomarkers and biochemical risk indicators for more comprehensive cardiovascular risk assessment [15]. This approach may enhance early identification of high-risk individuals and allow timely lifestyle and therapeutic interventions to lessen the burden of subsequent cardiovascular events [16]. In Pakistan, cardiovascular diseases (CVD) continue to be the primary cause of morbidity and mortality, with a rising prevalence observed at younger ages compared to Western populations [17]. Early identification of at-risk individuals, particularly among asymptomatic adults, is therefore a critical public health priority in Pakistan [18]. CT-based CAC scoring allows early risk stratification before the onset of clinical symptoms [19]. However, its use in routine screening within resource-limited settings such as Pakistan necessitates the identification of complementary and cost-effective biochemical markers [20]. Elevated serum homocysteine levels are commonly observed in South Asian populations, potentially due to nutritional deficiencies (particularly folate and vitamin B12), genetic predisposition, and lifestyle factors prevalent in Pakistan [21].

Although coronary artery calcification (CAC) is a well-established marker of subclinical atherosclerosis and cardiovascular risk, limited data exist regarding its association with serum homocysteine levels in asymptomatic populations, particularly in developing countries. Previous studies have primarily focused on symptomatic patients or individuals with established cardiovascular disease, leaving a gap in understanding the relationship between homocysteine and early coronary atherosclerosis among apparently healthy adults. Furthermore, regional epidemiological data examining biochemical risk markers alongside imaging-based indicators of coronary artery disease remain scarce. Homocysteine has been recognized as an emerging cardiovascular risk factor that may contribute to endothelial dysfunction, oxidative stress, and vascular inflammation, all of which play key roles in the development of atherosclerosis. Coronary artery calcification detected by non-contrast CT serves as a reliable imaging biomarker of coronary plaque burden and future cardiovascular risk. Investigating the relationship between serum homocysteine levels and CAC in asymptomatic individuals may provide valuable insights into early cardiovascular risk assessment and help identify individuals who may benefit from preventive interventions. This study aimed to

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evaluate the association between CT-detected coronary artery calcification and serum homocysteine levels in asymptomatic adults. It was hypothesized that higher serum homocysteine levels are associated with increased coronary artery calcification, reflecting a greater burden of subclinical atherosclerosis. This study aimed to investigate the correlation between serum homocysteine levels and the degree of coronary artery calcification in the Pakistani population, as well as the association between CT-detected coronary artery calcification and serum homocysteine levels in the asymptomatic population.

METHODS

To assess the relationship between blood homocysteine levels and CT-detected coronary artery calcification (CAC) in asymptomatic individuals in the Pakistani adult population, a cross-sectional analytical investigation was carried out. The study was carried out at Shahida Islam Medical College & Teaching Hospital, Lodhran, Pakistan, for a period of six months, June 2025 to November 2025, after taking approval from the institutional review board IRB letter number: SIMC/ET.C/003/0009/01/25 approved on 6th June 2025. Asymptomatic adults of either gender, aged 30–65 years, presenting for routine health screening were enrolled after obtaining informed consent. Individuals with a prior history of coronary artery disease, myocardial infarction, stroke, chronic kidney or liver disease, inflammatory conditions, pregnancy, or those receiving folate or vitamin B12 supplementation were excluded to minimize confounding factors. For the calculation of sample size, OpenEPI software was used, which is a freely available, authentic online tool. Keeping 50 % prevalence of CAC, 95 % confidence level, and 5 % confidence limits, the sample size came out to be 384. Therefore, using a non-probability convenience sampling technique, 384 participants visiting the outpatient clinic were included in the study. After recruitment, a systematic proforma was used to capture clinical and demographic information, such as age, gender, body mass index, smoking status, and the relevant medical history of participants. For coronary artery calcium scoring, non-contrast computed tomography was performed on each participant. Using the Agatston scoring system, coronary artery calcification was measured and classified as no calcification (score 0), mild (1–99), moderate (100–399), or severe (≥400). Serum homocysteine levels were assessed in a laboratory using a standardized enzymatic or immunoassay method after venous blood samples were obtained aseptically. Homocysteine levels were classified as normal or elevated according to established reference ranges. Coronary artery calcification was assessed using non-contrast cardiac computed tomography (CT). This technique detects calcified plaques in the coronary arteries based on their high radiographic density compared with surrounding tissues. During image acquisition, calcified lesions are identified as areas with attenuation values greater than 130 Hounsfield units (HU) and covering at least three contiguous pixels. The extent of coronary calcification was quantified using the Agatston scoring method, in which the area of each calcified lesion is multiplied by a weighting factor based on peak CT attenuation (130–199 HU=1, 200–299 HU=2, 300–399 HU=3, and ≥400 HU=4). The scores from all coronary artery segments are then summed to obtain the total coronary artery calcium (CAC) score, which reflects the overall burden of coronary atherosclerotic calcification. The patients were selected from the Department of Medicine (including patients referred to Radiology for a CT scan and Hematology Lab for Serum Homocysteine level. Data collection was carried out by the principal investigator (mentioned in author contributions). A CT scan was carried out by the Department of Radiology and was also reported and interpreted by an expert radiologist with at least 5 years of experience.

The SPSS, version 23.0 was used for data entry and analysis. Laboratory, clinical, and demographic characteristics were summarized using descriptive statistics. Categorical variables were displayed as frequencies and percentages, whilst continuous variables were given as mean ± standard deviation. The association between serum homocysteine levels and coronary artery calcification scores was assessed using the Pearson correlation coefficient. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

The baseline characteristics of research participants based on their Coronary Artery Calcification (CAC) status. The mean age of participants with no calcification was 44.8 ± 8.6 years, while that of participants with calcification was 56.2 ± 9.4 years, with a significant association of $p<0.001$. Systolic blood pressure, total cholesterol, LDL-C, HDL-C, triglycerides, and serum homocysteine showed a significant association of $p<0.001$ with CAC status. BMI, diastolic blood pressure, fasting glucose levels, and smoking status also showed a significant association of $p=0.05$, $p=0.04$, $p=0.02$, and $p=0.001$, respectively, with CAC status. Gender was found to be insignificantly associated with CAC status (Table 1).

Table 1: Baseline Characteristics of Study Participants According to Coronary Artery Calcification (CAC) Status

Variables	CAC = 0 (No Calcification) (n =224)	CAC > 0 (Calcification Present) (n = 160)	p-value
Age (Years)	44.8 ± 8.6	56.2 ± 9.4	<0.001
Male Gender, n (%)	102 (45.5 %)	104 (65 %)	0.038

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BMI (kg/m^2)	25.6 ± 3.9	28.4 ± 4.2	0.050
Systolic BP (mmHg)	122.4 ± 12.6	134.8 ± 15.2	<0.001
Diastolic BP (mmHg)	78.2 ± 8.4	84.1 ± 9.6	0.040
Fasting Glucose (mg/dL)	107.77 ± 21.51	121.65 ± 33.67	0.020
Total Cholesterol (mg/dL)	182.6 ± 32.4	205.8 ± 38.6	<0.001
LDL-C (mg/dL)	108.2 ± 26.4	132.6 ± 31.2	<0.001
HDL-C (mg/dL)	46.8 ± 9.2	41.4 ± 8.6	<0.001
Triglycerides (mg/dL)	142.3 ± 58.6	176.2 ± 72.4	<0.001
Serum Homocysteine (µmol/L)	9.8 ± 2.6	15.6 ± 4.2	<0.001
Smoking Status (Current), n (%)	38 (17 %)	52 (32.5 %)	0.001

In 224 participants with no CAC, mean serum homocysteine levels were found to be 9.8 ± 2.6 µmol/L. In 64 patients with mild CAC (1-99), mean serum homocysteine levels were 13.2 ± 3.4 µmol/L. In 58 patients with moderate CAC (100-399), mean serum homocysteine levels were 16.1 ± 3.8 µmol/L. In 38 patients with severe CAC (>400), mean serum homocysteine levels were 19.4 ± 4.6µmol/L. A significant association was observed between CAC score categories and serum homocysteine levels (Table 2).

Table 2: Serum Homocysteine Levels Across Coronary Artery Calcification Severity (n=384)

CAC Category (Agatston Score)	N	Serum Homocysteine (µmol/L)	p-value
CAC=0	224	9.8 ± 2.6	<0.001
CAC 1-99 (Mild)	64	13.2 ±3.4	
CAC 100-399 (Moderate)	58	16.1 ± 3.8	
CAC >400 (Severe)	38	19.4 ± 4.6	

The graphical representation demonstrates significantly higher serum homocysteine levels in asymptomatic adults with CT-detected coronary artery calcification compared to those without calcification (Figure 1).

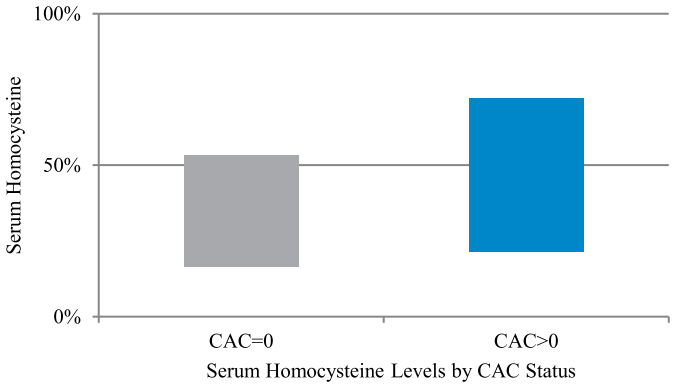

Figure 1: Comparison of Serum Homocysteine Levels by CAC Status

Scatter plot showing a positive correlation (r=0.82, p<0.001) between coronary artery calcium score and serum homocysteine levels in asymptomatic adults, indicating increasing homocysteine concentration with greater calcific burden (Figure 2).

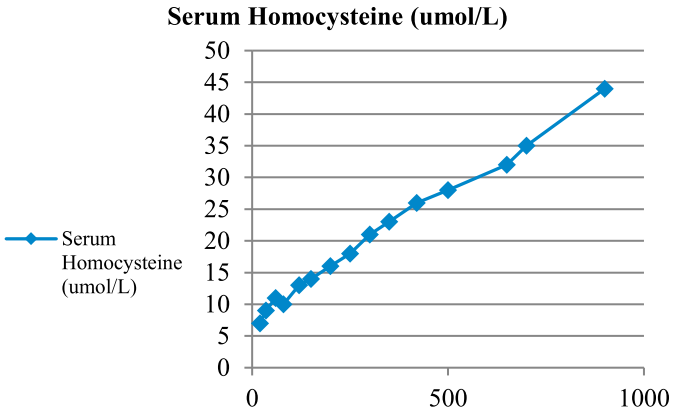

Figure 2: Correlation between Coronary Artery Calcium Score and Serum Homocysteine Level (r=0.82- indicating a strong correlation, p<0.001)

DISCUSSION

The findings of this research showed a significant association between CT—detected CAC as well as serum homocysteine levels among asymptomatic adults with CAC. 160 (41.7 %) out of 384 asymptomatic adults were found to have CAC. Our study also reported that sub-clinical atherosclerosis was a common entity even in asymptomatic adults. Furthermore, CAC was more commonly observed among older adults, predominantly males, concluding that age and male gender remained a strong non-modifiable determinant of CAC. Other factors, such as higher BMI, blood pressure, triglycerides, LDL, and lower HDL levels, were reported to have CAC, thereby clustering the fact that classical cardiac and metabolic risk factors were in line with CT findings of CAC and serum homocysteine. Elevated levels of CAC were strongly linked with CAC, demonstrating a dose-response relationship which supports its biological plausibility. The higher the level of serum homocysteine, the greater the burden of calcification. Consequently, homocysteine may be considered a marker of subclinical atherosclerosis. Similar to the findings of our study, Liaquat *et al.* in a local study, investigated the use of coronary artery calcium scoring through CT scan risk stratification. A substantial positive correlation between CAC and coronary artery stenosis (on CT scan) was discovered among the 1014 participants included in the study. In addition, age above 45 years, diabetes, and hypertension were all substantially linked to an increased risk of CAC [22]. Likewise, Van *et al.* in their research highlighted that CAC scoring can be of great value in guiding clinical management, especially in asymptomatic cases of CAC using a simple non-contrast CT. This further highlights the significance of our study, which is in line with the above-reported literature [23]. In accordance with our study findings, Karger *et al.* conducted a MESA (Multi-ethnic Study of Atherosclerosis) to examine the relationship between elevated serum

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homocysteine and calcification and its significance as a cardiovascular risk factor. The study found that elevated serum homocysteine levels may be a risk factor for the advancement of coronary artery calcification [15]. Similarly, another research by Jung et al, in their study on the identification and prevention of modifiable risk factors for cardiovascular diseases. The study observed that higher levels of homocysteine were linked to calcified plaques and vascular calcifications [24]. In yet another study by Jung *et al.* serum homocysteine levels were significantly associated with increased coronary artery calcification[25].

Although the findings of this research were in line with the published literature, this was one-of-a-kind research in the local population evaluating both CT- scan associated CAC as well as serum homocysteine levels. Limitations of the study were a single-center study with a limited sample size, with limited generalizability. The findings of this study have important clinical and public health implications. The observed association between elevated serum homocysteine levels and coronary artery calcification suggests that homocysteine may serve as a useful biochemical marker for identifying individuals at increased risk of subclinical atherosclerosis. Incorporating serum homocysteine assessment alongside imaging-based measures such as CT-detected coronary artery calcification could enhance early cardiovascular risk stratification in asymptomatic adults. Early identification of high-risk individuals may facilitate timely preventive strategies, including lifestyle modification and targeted medical interventions, potentially reducing the future burden of cardiovascular disease. This study has several limitations that should be considered when interpreting the findings. Further research should also evaluate additional biochemical and inflammatory markers along with nutritional factors such as vitamin B12 and folate, to better understand the underlying mechanisms and potential preventive strategies.

CONCLUSIONS

In asymptomatic individuals, elevated blood homocysteine is independently linked to the existence and degree of coronary artery calcification shown on CT. According to these results, homocysteine may be a helpful biomarker for identifying those who are more likely to develop subclinical coronary atherosclerosis.

Authors' Contribution

Conceptualization: MS
Methodology: SA
Formal analysis: WA, SLA, KA
Writing and Drafting: SA, SLA, SI
Review and Editing: MS, SA, WA, SLA, KA, SI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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